Patent Application
Docket No.: PC25512A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

In re Application of: GRIFFITH, DAVID A.	
	Group Art Unit: 1624
Serial No.: 10/763,105 Filed: January 21, 2004	Examiner: BALASUBRAMANIAN, VENKATARAMAN
For: CANNABINOID RECEPTOR LIGANDS AND USES THEREOF	

APPEAL BRIEF

Appeal Brief - Patents
Hon. Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This is an appeal from the Office Action mailed on May 14, 2007, finally rejecting claims 1-9, 11-16, 18, 21-26, 28-34, 56, 58-80 and 97; objecting to claims 10, 17, 19, 20, 27, 35 and 36; and allowing Claims 101, 108, 120 and 121, all the claims remaining in the Application.

Please charge to Deposit Account No.16-1445 the $500.00 to cover the fee for the appeal and any additional fees or adjustments to the fee for the appeal.

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REAL PARTY IN INTEREST

This Application is assigned to Pfizer Inc., a U.S. Corporation organized under the laws of the State of Delaware and having its headquarters at 235 East 42nd Street, New York, New York USA.

RELATED INTERFERENCES AND APPEALS

The subject matter of this Appeal is not related to any co-pending Interferences or Appeals in the U.S. Patent & Trademark Office.

STATUS OF CLAIMS

1. Claims 1-36, 56, 58-80, 97, 101, 108, 120 and 121 remain in the application.

2. Claims 37-55, 57, 81-96, 98-100, 102-107, 109-119 were previously canceled without prejudice.

3. Claims 1-9, 11-16, 18, 21-26, 28-34, 56, 58-80 and 97 have been finally rejected under 35 U.S.C. §103(a) as being unpatentable over Gudmundsson, et al., WO 03/076441.

4. Claims 10, 17, 19, 20, 27, 35 and 36 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claims and any intervening claims.

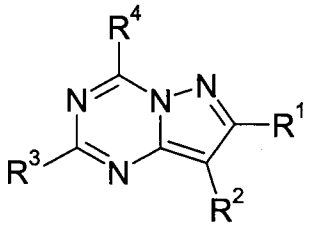
5. Claims 101, 108, 120 and 121 are allowed.

STATUS OF AMENDMENTS

All amendments in this Application have been entered without objection.

SUMMARY OF CLAIMED SUBJECT MATTER

The present invention provides, in Claim 1 and its dependent claims, a compound of Formula (I) that act as cannabinoid receptor ligands (in particular, CB1 receptor antagonists). (page 3, lines 30-31)



(I)

wherein

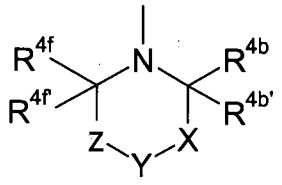
R^1 is an optionally substituted aryl or an optionally substituted heteroaryl (preferably, R^1 is a substituted phenyl, more preferably a phenyl substituted with one to three substituents independently selected from the group consisting of halo (preferably, chloro or fluoro), (C_1-C_4)alkoxy, (C_1-C_4)alkyl, halo-substituted (C_1-C_4)alkyl (preferably fluoro-substituted alkyl), and cyano, most preferably, R^1 is 2-chlorophenyl, 2-fluorophenyl, 2,4-dichlorophenyl, 2-fluoro-4-chlorophenyl, 2-chloro-4-fluorophenyl, or 2,4-difluorophenyl);

R^2 is an optionally substituted aryl (preferably, R^2 is a substituted phenyl, more preferably a phenyl substituted with one to three substituents independently selected from the group consisting of halo (preferably, chloro or fluoro), (C_1-C_4)alkoxy, (C_1-C_4)alkyl, halo-substituted (C_1-C_4)alkyl (preferably fluoro-substituted alkyl), and cyano, most preferably, R^2 is 4-chlorophenyl or 4-fluorophenyl);

R^3 is hydrogen, (C_1-C_4)alkyl, halo-substituted (C_1-C_4)alkyl, or (C_1-C_4)alkoxy;

R^4 is

(i) a group having Formula (IA)



IA

where

R^{4b} and $R^{4b'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, $(C_1-C_4)alkyl)_2N$-C(O)-, (C_1-C_6)alkylamino-, $((C_1-C_4)alkyl)_2$amino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or either R^{4b} or $R^{4b'}$ taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge, or an ethylene bridge;

X is a bond, $-CH_2CH_2-$ or $-C(R^{4c})(R^{4c'})-$, where R^{4c} and $R^{4c'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, $((C_1-C_4)alkyl)_2N$-C(O)-, (C_1-C_6)alkylamino-, di(C_1-C_4)alkylamino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or either R^{4c} or $R^{4c'}$ taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge or an ethylene bridge;

Y is oxygen, sulfur, -C(O)-, or $-C(R^{4d})(R^{4d'})-$, where R^{4d} and $R^{4d'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, $((C_1-C_4)alkyl)_2N$-C(O)-, (C_1-C_6)alkylamino-, di(C_1-C_4)alkylamino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or R^{4d} and $R^{4d'}$ taken together form a 3-6 membered partially or fully saturated heterocyclic ring, a 5-6 membered lactone ring, or a 4-6 membered lactam ring, where said heterocyclic ring, said lactone ring and said lactam ring are optionally substituted with one or more substituents and said lactone ring and said lactam ring optionally contain an additional heteroatom selected from oxygen, nitrogen or sulfur, or

Y is $-NR^{4d''}-$, where $R^{4d''}$ is a hydrogen or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_3)alkylsulfonyl-, (C_1-C_3)alkylaminosulfonyl-, di(C_1-C_3)alkylaminosulfonyl-, acyl, (C_1-C_6)alkyl-O-C(O)-, aryl, and heteroaryl, where said moiety is optionally substituted with one or more substituents;

Z is a bond, $-CH_2CH_2-$, or $-C(R^{4e})(R^{4e'})-$, where R^{4e} and $R^{4e'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)-$, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, $((C_1-C_4)alkyl)_2N-C(O)-$, (C_1-C_6)alkylamino-, di(C_1-C_4)alkylamino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or either R^{4e} or $R^{4e'}$ taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge or an ethylene bridge; and

R^{4f} and $R^{4f'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)-$, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, $((C_1-C_4)alkyl)_2N-C(O)-$, (C_1-C_6)alkylamino-, di(C_1-C_4)alkylamino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

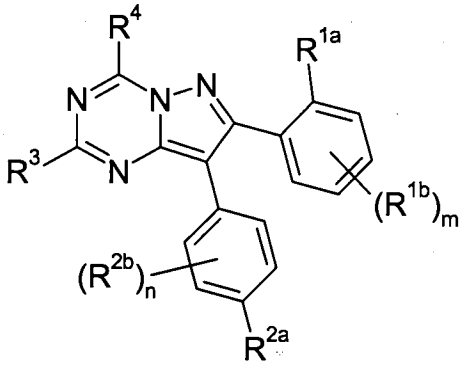
or either R^{4f} or $R^{4f'}$ taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge or an ethylene bridge;

a pharmaceutically acceptable salt thereof.

(page 4, line 1 through page 8, line 7).

The definition of R^4 was limited to a group having Formula (IA) in an amendment received in the USPTO on September 6, 2005 in response to a restriction requirement mailed on August 26, 2005. The references to prodrugs and solvates were deleted in an amendment received in the USPTO on May 23, 2006. The reference to hydrates and R^2 as an optionally substituted heteroaryl was deleted in an amendment received in the USPTO on July 13, 2006.

The present invention also provides, in Claim 56 and its dependent claims, a compound of Formula II



(II)

wherein

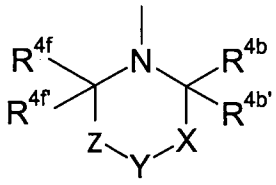
R^{1a}, R^{1b}, R^{2a}, and R^{2b} are each independently halo, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$alkyl, halo-substituted $(C_1\text{-}C_4)$alkyl, or cyano;

n and m are each independently 0, 1 or 2;

R^3 is hydrogen, $(C_1\text{-}C_4)$alkyl, halo-substituted $(C_1\text{-}C_4)$alkyl, or $(C_1\text{-}C_4)$alkoxy; and

R^4 is

(i) a group having Formula (IA)



IA

where R^{4a} is hydrogen or $(C_1\text{-}C_3)$alkyl;

R^{4b} and $R^{4b'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, (C_1-C_4)alkyl$)_2$N-C(O)-, (C_1-C_6)alkylamino-, $((C_1-C_4)$alkyl$)_2$amino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or either R^{4b} or $R^{4b'}$ taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge, or an ethylene bridge;

X is a bond, $-CH_2CH_2-$ or $-C(R^{4c})(R^{4c'})-$, where R^{4c} and $R^{4c'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, $((C_1-C_4)$alkyl$)_2$N-C(O)-, (C_1-C_6)alkylamino-, di(C_1-C_4)alkylamino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or either R^{4c} or $R^{4c'}$ taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge or an ethylene bridge;

Y is oxygen, sulfur, -C(O)-, or $-C(R^{4d})(R^{4d'})-$, where R^{4d} and $R^{4d'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, $((C_1-C_4)$alkyl$)_2$N-C(O)-, (C_1-C_6)alkylamino-, di(C_1-C_4)alkylamino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or R^{4d} and $R^{4d'}$ taken together form a 3-6 membered partially or fully saturated carbocyclic ring, a 3-6 membered partially or fully saturated heterocyclic ring, a 5-6 membered lactone ring, or a 4-6 membered lactam ring, where the carbocyclic ring, the

heterocyclic ring, the lactone ring and the lactam ring are optionally substituted with one or more substituents and the lactone ring and the lactam ring optionally contain an additional heteroatom selected from oxygen, nitrogen or sulfur, or

Y is $-NR^{4d''}-$, where $R^{4d''}$ is a hydrogen or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_3)alkylsulfonyl-, (C_1-C_3)alkylaminosulfonyl-, di(C_1-C_3)alkylaminosulfonyl-, acyl, (C_1-C_6)alkyl-O-C(O)-, aryl, and heteroaryl, where said moiety is optionally substituted with one or more substituents;

Z is a bond, $-CH_2CH_2-$, or $-C(R^{4e})(R^{4e'})-$, where R^{4e} and $R^{4e'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)-$, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, $((C_1-C_4)alkyl)_2N-C(O)-$, (C_1-C_6)alkylamino-, di(C_1-C_4)alkylamino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or either R^{4e} or $R^{4e'}$ taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge or an ethylene bridge; and

R^{4f} and $R^{4f'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)-$, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, $((C_1-C_4)alkyl)_2N-C(O)-$, (C_1-C_6)alkylamino-, di(C_1-C_4)alkylamino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or either R^{4f} or $R^{4f'}$ taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge or an ethylene bridge;

a pharmaceutically acceptable salt thereof. (page 8, line 8 through page 12, line 3) The definition of R^4 was limited to a group having Formula (IA) in an amendment received in the USPTO on September 6, 2005 in response to a restriction requirement mailed on August 26, 2005. The references to prodrugs and solvates were deleted in an amendment received in the

USPTO on May 23, 2006. The reference to hydrates was deleted in an amendment received in the USPTO on July 13, 2006.

The present invention further provides, in Claim 97, a composition comprising (1) a compound of Claim 1, or a pharmaceutically acceptable salt thereof; and (2) a pharmaceutically acceptable excipient, diluent, or carrier. (page 28, lines 14-16)

GROUNDS OF REJECTIONS TO BE REVIEWED ON APPEAL

I. The general issue on Appeal is whether the Examiner erred in rejecting Claims 1-6, 11-14, 21-23, 28-31, and 97 under 35 U.S.C. §103(a) as being unpatentable over Gudmundsson, et al., WO 03/076441 ("Gudmundsson").

II. The general issue on Appeal is whether the Examiner erred in rejecting Claims 7-9, 15, 16, 18, 24-26, 32-34, 56, and 58-80 under 35 U.S.C. §103(a) as being unpatentable over Gudmundsson, et al., WO 03/076441 ("Gudmundsson").

ARGUMENTS OF APPELLANTS

I. *Claims 1-6, 11-14, 21-23, 28-31, and 97 have been finally rejected under 35 U.S.C. §103(a) as being unpatentable over Gudmundsson, et al., WO03/076441.*

The Examiner based the rejection on the reasons set forth in the Office Action mailed on May 14, 2007 and repeated in the Advisory Action mailed on June 28, 2007 which states that the Gudmundsson compounds are closely related to the compounds of the present invention as being positional isomers and are therefore not deemed patentable. This is clearly contrary to established case law. In *Takeda Chemical vs. Alphapharm* (Fed Cir., No. 06-1329, 2007), the court states that "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." The court found that because there was no motivation in the prior art for selecting the earlier compound as the lead compound for research, the burden for proving a prima facie case of obviousness based on a structurally similar compound was not met. The Examiner asserts that homolog, analog or isomers of the prior art compounds would have similar properties and would therefore it would be obvious to make them. This is clearly contrary to the findings of the Takeda court.

> "Our case law concerning prima facie obviousness of structurally similar compounds is well-established. We have held that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." Dillion, 919 F.2d at 691. In addition to structural similarity between the compounds, ***a prima facie case of obviousness also requires a showing of "adequate support in the prior art" for the change in structure***. In re Grabiak, 769 F.2d 729, 731-32 (Fed Cir. 1985).
>
> We elaborated on this requirement in the case of In re Deuel, 51 F.3d 1552, 1558 (Fed. Cir. 1995), where we stated that "[n]ormally a prima facie case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." Id. A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." Id. We clarified, however, that in order find a prima facie case of unpatentability in such instances, ***a showing that the "prior art would have***

> ***suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required***. Id. (citing In re Jones, 958 F.2d 247 (Fed Cir. 1992), 919 R.2d 688; Grabiak, 769 F.2d 729; In re Lalu, 747 F.2d 703 (Fed Cir. 1984)).
>
> That test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in KSR. While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant filed to combine the elements in the way the claimed new invention does" in an obviousness determination. KSR, 127 S.Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the Graham analysis." Id. As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. Id. Thus, ***in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound***." (Emphasis added) *Takeda Chemical vs. Alphapharm* (Fed Cir., No. 06-1329, 2007)

The Examiner provided no evidence that the prior art compounds having the particular substituents on the pyrazolo rings would have been chosen as lead compounds. The Examiner particularly pointed out Examples 6 and 31 and asserted that exchanging the aryl and heteroaryl groups would result in the instant compounds. The Gudmundsson compounds of Example 6 and 31 are pyrazolo[1,5-c]pyrimidinyl derivatives; whereas, the compounds of the present invention are pyrazolo[1,5-a][1,3,5]triazine derivatives. Clearly, exchanging the aryl and heteroaryl groups would not lead to the instant compounds. Pyrazolo[1,5-c]pyrimidinyl derivatives and pyrazolo[1,5-a][1,3,5]triazine derivatives are not positional isomers.

Even if a preliminary showing could be made, the Examiner failed to show that there existed a reason, based on what was known at the time of the invention, to make the chemical modifications necessary to achieve the claimed compounds. Instead, the Examiner merely asserts that "positional isomers are not deemed patentably distinct absent evidence of superior or unexpected properties." This is clearly contrary to the case law outlined above. Therefore, Examiner has failed to meet his burden for showing a prima facie case of obviousness.

Even if one could argue that the Examiner met his prima facie case, through his own admissions, the Examiner recognizes that evidence of superior or unexpected properties can overcome an obviousness rejection based on positional isomers. However, the Examiner refused to accept the fact that the present compounds which act as CB-1 receptor antagonists provides evidence of unexpected properties as compared to the Gudmundsson compounds

which are used in the treatment of herpes viral infections. Clearly, compounds used in the prophylaxis or treatment of a herpes viral infection do not possess the same or similar properties of compounds which act as CB-1 receptor antagonists. It would not be reasonable to expect that modifications to compounds that are useful for the treatment of herpes would bind to a CB-1 receptor and act as an antagonist at that receptor. Examiner has provided no additional evidence that would show a reasonable expectation that pyrazolotriazine derivatives would be useful for treating diseases modulated by the antagonism of the CB-1 receptor and therefore has provided no evidence that Applicant would have been motivated to make the asserted changes to the Gudmundsson compounds in the design of CB-1 receptor antagonists.

II. *Claims 7-9, 15, 16, 18, 24-26, 32-34, 56, and 58-80 have been finally rejected under 35 U.S.C. §103(a) as being unpatentable over Gudmundsson, et al., WO03/076441.*

Similar to Claim 1 (and dependents thereof), the Examiner based the rejection of Claims 7-9, 15, 16, 18, 24-26, 32-34, 56, and 58-80 on the reasons set forth in the Office Action mailed on May 14, 2007 and repeated in the Advisory Action mailed on June 28, 2007 which states that the Gudmundsson compounds are closely related to the compounds of the present invention as being positional isomers and are therefore not deemed patentable. As argued above, this is clearly contrary to current case law. In addition, the Examiner provides no explanation as to why this particular embodiment would be obvious. Gudmundsson provides no guidance or reason to make pyrazolo[1,5-a][1,3,5]triazine compounds having phenyl substituents at both the R1 and R2 positions and, in particular, to make the specific substitution patterns on the phenyl rings (e.g., R^{1a}, R^{1b}, R^{2a} and R^{2b}) which provide preferred embodiments of the present invention. More importantly, the compounds of the present invention where R1 and R2 are both phenyl groups are not positional isomers of the Gudmundsson compounds as asserted by the Examiner. The Gudmundsson compounds have a heteroaryl and an aryl group adjacent to each other on the pyrazolotriazine ring structure; therefore, they cannot be positional isomers.

In addition, the Examiner has provided no additional evidence that would show a reasonable expectation that the pyrazolotriazine derivatives would be useful for treating diseases modulated by the antagonism of the CB-1 receptor and therefore has provided no

evidence that Applicant would have been motivated to make the asserted changes to the Gudmundsson compounds in the design of CB-1 receptor antagonists.

Conclusion

Based on the arguments presented above, Applicant respectfully submits that Claims 1-36, 56, 58-80 and 97, in addition to Claims 101, 108, 120 and 121, are in condition for allowance.

Respectfully Submitted By:

July 9, 2007

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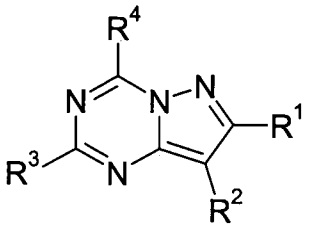
CLAIMS APPENDIX

1(previously presented). A compound of Formula (I)



(I)

wherein

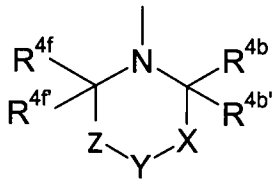
R^1 is an optionally substituted aryl or an optionally substituted heteroaryl;

R^2 is an optionally substituted aryl;

R^3 is hydrogen, $(C_1\text{-}C_4)$alkyl, halo-substituted $(C_1\text{-}C_4)$alkyl, or $(C_1\text{-}C_4)$alkoxy;

R^4 is

(i) a group having Formula (IA)



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where

R^{4b} and $R^{4b'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, acyloxy, acyl, $(C_1\text{-}C_3)$alkyl-O-C(O)-, $(C_1\text{-}C_4)$alkyl-NH-C(O)-, $(C_1\text{-}C_4)$alkyl$)_2$N-C(O)-, $(C_1\text{-}C_6)$alkylamino-, $((C_1\text{-}C_4)$alkyl$)_2$amino-, $(C_3\text{-}C_6)$cycloalkylamino-, acylamino-, aryl$(C_1\text{-}C_4)$alkylamino-, heteroaryl$(C_1\text{-}C_4)$alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or either R^{4b} or $R^{4b'}$ taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge, or an ethylene bridge;

X is a bond, $-CH_2CH_2-$ or $-C(R^{4c})(R^{4c'})-$, where R^{4c} and $R^{4c'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)-$, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, $((C_1-C_4)alkyl)_2N-C(O)-$, (C_1-C_6)alkylamino-, di(C_1-C_4)alkylamino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or either R^{4c} or $R^{4c'}$ taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge or an ethylene bridge;

Y is oxygen, sulfur, -C(O)-, or $-C(R^{4d})(R^{4d'})-$, where R^{4d} and $R^{4d'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)-$, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, $((C_1-C_4)alkyl)_2N-C(O)-$, (C_1-C_6)alkylamino-, di(C_1-C_4)alkylamino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or R^{4d} and $R^{4d'}$ taken together form a 3-6 membered partially or fully saturated heterocyclic ring, a 5-6 membered lactone ring, or a 4-6 membered lactam ring, where said heterocyclic ring, said lactone ring and said lactam ring are optionally substituted with one or more substituents and said lactone ring and said lactam ring optionally contain an additional heteroatom selected from oxygen, nitrogen or sulfur, or

Y is $-NR^{4d''}-$, where $R^{4d''}$ is a hydrogen or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_3)alkylsulfonyl-, (C_1-C_3)alkylaminosulfonyl-, di(C_1-C_3)alkylaminosulfonyl-, acyl, (C_1-C_6)alkyl-O-C(O)-, aryl, and heteroaryl, where said moiety is optionally substituted with one or more substituents;

Z is a bond, $-CH_2CH_2-$, or $-C(R^{4e})(R^{4e'})-$, where R^{4e} and $R^{4e'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)-$, or a chemical moiety

selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, acyloxy, acyl, $(C_1\text{-}C_3)$alkyl-O-C(O)-, $(C_1\text{-}C_4)$alkyl-NH-C(O)-, $((C_1\text{-}C_4)\text{alkyl})_2$N-C(O)-, $(C_1\text{-}C_6)$alkylamino-, di$(C_1\text{-}C_4)$alkylamino-, $(C_3\text{-}C_6)$cycloalkylamino-, acylamino-, aryl$(C_1\text{-}C_4)$alkylamino-, heteroaryl$(C_1\text{-}C_4)$alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

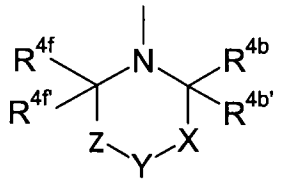
or either R^{4e} or $R^{4e'}$ taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge or an ethylene bridge; and

R^{4f} and $R^{4f'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, acyloxy, acyl, $(C_1\text{-}C_3)$alkyl-O-C(O)-, $(C_1\text{-}C_4)$alkyl-NH-C(O)-, $((C_1\text{-}C_4)\text{alkyl})_2$N-C(O)-, $(C_1\text{-}C_6)$alkylamino-, di$(C_1\text{-}C_4)$alkylamino-, $(C_3\text{-}C_6)$cycloalkylamino-, acylamino-, aryl$(C_1\text{-}C_4)$alkylamino-, heteroaryl$(C_1\text{-}C_4)$alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or either R^{4f} or $R^{4f'}$ taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge or an ethylene bridge;

a pharmaceutically acceptable salt thereof.

2(previously presented). The compound of Claim 1 wherein R^4 is a group having Formula (IA)



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where,

R^{4b} and $R^{4b'}$ are each independently hydrogen, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of $(C_1\text{-}C_6)$alkyl, acyl, $(C_1\text{-}C_3)$alkyl-O-C(O)-, $(C_1\text{-}C_4)$alkyl-NH-C(O)-, $(C_1\text{-}C_4)\text{alkyl})_2$N-C(O)-, aryl, heteroaryl, a partially or fully saturated 3-6 membered heterocycle,

and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or R^{4b} or $R^{4b'}$ taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge, or an ethylene bridge;

X is a bond, $-CH_2CH_2-$ or $-C(R^{4c})(R^{4c'})-$, where R^{4c} is hydrogen, cyano, hydroxy, amino, $H_2NC(O)-$, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, $(C_1-C_4)alkyl)_2N-C(O)-$, (C_1-C_6)alkylamino-, $((C_1-C_4)alkyl)_2$amino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or R^{4c} taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge, or an ethylene bridge, and

$R^{4c'}$ is hydrogen, $H_2NC(O)-$, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, $(C_1-C_4)alkyl)_2N-C(O)-$, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or $R^{4c'}$ taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge, or an ethylene bridge;

Y is oxygen, sulfur, -C(O)-, or $-C(R^{4d})(R^{4d'})-$, where R^{4d} is hydrogen, cyano, hydroxy, amino, $H_2NC(O)-$, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, $(C_1-C_4)alkyl)_2N-C(O)-$, (C_1-C_6)alkylamino-, $((C_1-C_4)alkyl)_2$amino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents, and

$R^{4d'}$ is hydrogen, $H_2NC(O)-$, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, $(C_1-C_4)alkyl)_2N-C(O)-$, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered

partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or R^{4d} and $R^{4d'}$ taken together form a 3-6 membered partially or fully saturated heterocyclic ring, a 5-6 membered lactone ring, or a 4-6 membered lactam ring, where said heterocyclic ring, said lactone ring and said lactam ring are optionally substituted with one or more substituents and said lactone ring and said lactam ring optionally contain an additional heteroatom selected from oxygen, nitrogen or sulfur, or

Y is $-NR^{4d''}-$, where $R^{4d''}$ is a hydrogen or a chemical moiety selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_3)$alkylsulfonyl-, $(C_1\text{-}C_3)$alkylaminosulfonyl-, di$(C_1\text{-}C_3)$alkylaminosulfonyl-, acyl, $(C_1\text{-}C_6)$alkyl-O-C(O)-, aryl, and heteroaryl, where said moiety is optionally substituted with one or more substituents;

Z is a bond, $-CH_2CH_2-$, or $-C(R^{4e})(R^{4e'})-$, where R^{4e} is hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, acyloxy, acyl, $(C_1\text{-}C_3)$alkyl-O-C(O)-, $(C_1\text{-}C_4)$alkyl-NH-C(O)-, $(C_1\text{-}C_4)$alkyl$)_2$N-C(O)-, $(C_1\text{-}C_6)$alkylamino-, $((C_1\text{-}C_4)$alkyl$)_2$amino-, $(C_3\text{-}C_6)$cycloalkylamino-, acylamino-, aryl$(C_1\text{-}C_4)$alkylamino-, heteroaryl$(C_1\text{-}C_4)$alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or R^{4e} taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge, or an ethylene bridge, and

$R^{4e'}$ is hydrogen, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of $(C_1\text{-}C_6)$alkyl, acyl, $(C_1\text{-}C_3)$alkyl-O-C(O)-, $(C_1\text{-}C_4)$alkyl-NH-C(O)-, $(C_1\text{-}C_4)$alkyl$)_2$N-C(O)-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or $R^{4e'}$ taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge, or an ethylene bridge; and

R^{4f} and $R^{4f'}$ are each independently hydrogen, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of $(C_1\text{-}C_6)$alkyl, acyl, $(C_1\text{-}C_3)$alkyl-O-C(O)-, $(C_1\text{-}C_4)$alkyl-NH-C(O)-, $(C_1\text{-}C_4)$alkyl$)_2$N-C(O)-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle,

and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or R^{4f} or $R^{4f'}$ taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge, or an ethylene bridge;

a pharmaceutically acceptable salt thereof.

3(previously presented). The compound of Claim of 2 wherein

R^1 and R^2 are each independently a substituted phenyl;

R^{4b} is hydrogen, an optionally substituted $(C_1\text{-}C_3)$alkyl, or taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge, or an ethylene bridge;

$R^{4b'}$ is hydrogen, an optionally substituted $(C_1\text{-}C_3)$alkyl, or taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge, or an ethylene bridge;

R^{4f} is hydrogen, an optionally substituted $(C_1\text{-}C_3)$alkyl, or taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge, or an ethylene bridge; and

$R^{4f'}$ is hydrogen, an optionally substituted $(C_1\text{-}C_3)$alkyl, or taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge, or an ethylene bridge;

a pharmaceutically acceptable salt thereof.

4(previously presented). The compound of Claim 3 wherein

X is $-C(R^{4c})(R^{4c'})-$, where R^{4c} and $R^{4c'}$ are each independently hydrogen, $H_2NC(O)$-, or a chemical moiety selected from $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_4)$alkyl-NH-C(O)-, or $((C_1\text{-}C_4)\text{alkyl})_2N\text{-}C(O)$-, where said moiety is optionally substituted with one or more substituents,

or either R^{4c} or $R^{4c'}$ taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge or an ethylene bridge;

Y is $-NR^{4d''}-$, where $R^{4d''}$ is a hydrogen or a chemical moiety selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_3)$alkylsulfonyl, $(C_1\text{-}C_3)$alkylaminosulfonyl, di$(C_1\text{-}C_3)$alkylaminosulfonyl, acyl, $(C_1\text{-}C_6)$alkyl-O-C(O)-, aryl, and heteroaryl, where said moiety is optionally substituted with one or more substituents;

Z is $-C(R^{4e})(R^{4e'})-$, where R^{4e} and $R^{4e'}$ are each independently hydrogen, $H_2NC(O)$-, or a chemical moiety selected from $C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_4)$alkyl-NH-C(O)-, or $((C_1\text{-}C_4)\text{alkyl})_2N\text{-}C(O)$-, where said moiety is optionally substituted with one or more substituents,

or either R^{4e} or $R^{4e'}$ taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge or an ethylene bridge;

a pharmaceutically acceptable salt thereof.

5(previously presented). The compound of Claim 4 wherein $R^{4d''}$ is a hydrogen or a chemical moiety selected from the group consisting of $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkylsulfonyl, $(C_1\text{-}C_3)$alkylaminosulfonyl, di$(C_1\text{-}C_3)$alkylaminosulfonyl, acyl, $(C_1\text{-}C_6)$alkyl-O-C(O)-, and heteroaryl, where said moiety is optionally substituted with one or more substituents;

a pharmaceutically acceptable salt thereof.

6(previously presented). The compound of Claim 5 wherein $R^{4d''}$ is a hydrogen or a chemical moiety selected from the group consisting of $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkylsulfonyl, $(C_1\text{-}C_3)$alkylaminosulfonyl, di$(C_1\text{-}C_3)$alkylaminosulfonyl, acyl, and $(C_1\text{-}C_6)$alkyl-O-C(O)-, where said moiety is optionally substituted with 1-3 fluorines,

or $R^{4d''}$ is a heteroaryl, where said heteroaryl is optionally substituted with 1 to 2 substituents independently selected from the group consisting of chloro, fluoro, $(C_1\text{-}C_3)$alkoxy, $(C_1\text{-}C_3)$alkyl, and fluoro-substituted $(C_1\text{-}C_3)$alkyl;

a pharmaceutically acceptable salt thereof.

7(previously presented). The compound of Claim 4, 5 or 6 wherein R^1 and R^2 are each independently a phenyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$alkyl, halo-substituted $(C_1\text{-}C_4)$alkyl, and cyano;

a pharmaceutically acceptable salt thereof.

8(previously presented). The compound of Claim 7 wherein R^1 and R^2 are each independently a phenyl substituted with 1 to 2 substituents independently selected from the group consisting of chloro, fluoro, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$alkyl, fluoro-substituted $(C_1\text{-}C_4)$alkyl), and cyano;

a pharmaceutically acceptable salt thereof.

9(previously presented). The compound of Claim 8 wherein R^1 is 2-chlorophenyl, 2-fluorophenyl, 2,4-dichlorophenyl, 2-fluoro-4-chlorophenyl, 2-chloro-4-fluorophenyl, or 2,4-difluorophenyl; and R^2 is 4-chlorophenyl or 4-fluorophenyl;

a pharmaceutically acceptable salt thereof.

10(previously presented). The compound of Claim 9 selected from the group consisting of

7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-4-(4-methylpiperazin-1-yl)-pyrazolo[1,5-a][1,3,5]triazine;

7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-4-(4-pyrimidin-2-ylpiperazin-1-yl)-pyrazolo[1,5-a][1,3,5]triazine;

7-(2-chlorophenyl)-8-(4-chlorophenyl)-4-[(1S,4S)-5-methanesulfonyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-methylpyrazolo[1,5-a][1,3,5]triazine;

7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-4-[4-(propane-2-sulfonyl)-piperazin-1-yl]-pyrazolo[1,5-a][1,3,5]triazine;

7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-4-(4-ethanesulfonyl)-piperazin-1-yl)-pyrazolo[1,5-a][1,3,5]triazine;

7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-4-piperazin-1-yl-pyrazolo[1,5-a][1,3,5]triazine;

7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-4-(4-methanesulfonyl)-piperazin-1-yl)-pyrazolo[1,5-a][1,3,5]triazine;

(1S,4S)-5-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester;

7-(2-chlorophenyl)-8-(4-chlorophenyl)-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-methylpyrazolo[1,5-a][1,3,5]triazine;

1-{(1S,4S)-5-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}-ethanone;

1-{(1S,4S)-5-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}-2-methylpropan-1-one;

1-{(1S,4S)-5-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}-phenylmethanone;

7-(2-chlorophenyl)-8-(4-chlorophenyl)-4-[(1S,4S)-5-ethanesulfonyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-methylpyrazolo[1,5-a][1,3,5]triazine;

7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-4-[(1S,4S)-5-(propane-2-sulfonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]-pyrazolo[1,5-a][1,3,5]triazine; and

(1S,4S)-5-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]- 2,5-diazabicyclo[2.2.1]heptane-2-sulfonic acid dimethylamide;

a pharmaceutically acceptable salt thereof.

11(previously presented). The compound of Claim 3 wherein Y is $-C(R^{4d})(R^{4d'})-$, where R^{4d} is hydrogen, cyano, hydroxy, amino, $H_2NC(O)-$, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, $(C_1-C_4)alkyl)_2N-C(O)-$, (C_1-C_6)alkylamino-, $((C_1-C_4)alkyl)_2$amino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

$R^{4d'}$ is hydrogen, $H_2NC(O)-$, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, $(C_1-C_4)alkyl)_2N-C(O)-$, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or R^{4d} and $R^{4d'}$ taken together form a 3-6 membered partially or fully saturated heterocyclic ring, a 5-6 membered lactone ring, or a 4-6 membered lactam ring, where said heterocyclic ring, said lactone ring and said lactam ring are optionally substituted with one or more substituents and said lactone ring and said lactam ring optionally contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

a pharmaceutically acceptable salt thereof.

12(previously presented). The compound of Claim 11 wherein

R^{4b}, $R^{4b'}$, R^{4f}, and $R^{4f'}$ are all hydrogen;

R^{4d} is amino, $(C_1\text{-}C_6)$alkylamino, di$(C_1\text{-}C_4)$alkylamino, $(C_3\text{-}C_6)$cycloalkylamino, acylamino, aryl$(C_1\text{-}C_4)$alkylamino-, heteroaryl$(C_1\text{-}C_4)$alkylamino-; and

$R^{4d'}$ is $(C_1\text{-}C_6)$alkyl, $H_2NC(O)$-, $(C_1\text{-}C_4)$alkyl-NH-C(O)-, or $((C_1\text{-}C_4)alkyl)_2N\text{-}C(O)$-, or aryl;

a pharmaceutically acceptable salt thereof.

13(previously presented). The compound of Claim 12 wherein

X is a bond or $-C(R^{4c})(R^{4c'})$-, where R^{4c} and $R^{4c'}$ are each hydrogen; and

Z is a bond or $-C(R^{4e})(R^{4e'})$-, where R^{4e} and $R^{4e'}$ are each hydrogen;

a pharmaceutically acceptable salt thereof.

14(previously presented). The compound of Claim 13 wherein R^{4d} is amino, $(C_1\text{-}C_6)$alkylamino, di$(C_1\text{-}C_4)$alkylamino, $(C_3\text{-}C_6)$cycloalkylamino; and

$R^{4d'}$ is $H_2NC(O)$-, $(C_1\text{-}C_4)$alkyl-NH-C(O)-, or $((C_1\text{-}C_4)alkyl)_2N\text{-}C(O)$-;

a pharmaceutically acceptable salt thereof.

15(previously presented). The compound of Claim 11, 12, 13 or 14 wherein R^1 and R^2 are each independently a phenyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$alkyl, halo-substituted $(C_1\text{-}C_4)$alkyl, and cyano;

a pharmaceutically acceptable salt thereof.

16(previously presented). The compound of Claim 15 wherein R^1 and R^2 are each independently a phenyl substituted with 1 to 2 substituents independently selected from the group consisting of chloro, fluoro, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$alkyl, fluoro-substituted $(C_1\text{-}C_4)$alkyl), and cyano;

a pharmaceutically acceptable salt thereof.

17(previously presented). The compound of Claim 16 selected from the group consisting of

1-[7-(2-chlorophenyl)-8-(2,4-dichlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-ethylaminoazetidine-3-carboxylic acid amide;

1-[7,8-bis-(2-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-ethylaminoazetidine-3-carboxylic acid amide;

1-[7-(2-chlorophenyl)-8-(4-cyanophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-ethylaminoazetidine-3-carboxylic acid amide;

1-[7-(2-chlorophenyl)-8-(4-methylphenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-ethylaminoazetidine-3-carboxylic acid amide;

1-[7-(2-chlorophenyl)-8-(4-ethylphenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-ethylaminoazetidine-3-carboxylic acid amide; and

1-[7-(2-chlorophenyl)-8-(4-methoxyphenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-ethylaminoazetidine-3-carboxylic acid amide;

a pharmaceutically acceptable salt thereof.

18(previously presented). The compound of Claim 16 wherein R^1 is 2-chlorophenyl, 2-fluorophenyl, 2,4-dichlorophenyl, 2-fluoro-4-chlorophenyl, 2-chloro-4-fluorophenyl, or 2,4-difluorophenyl; and R^2 is 4-chlorophenyl or 4-fluorophenyl;

a pharmaceutically acceptable salt thereof.

19(previously presented). The compound of Claim 18 selected from the group consisting of

1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-4-methylaminopiperidine-4-carboxylic acid amide;

1-[7-(2-chlorophenyl)-8-(4-fluorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-4-ethylaminopiperidine-4-carboxylic acid amide;

1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-4-ethylaminopiperidine-4-carboxylic acid amide;

1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-4-isopropylaminopiperidine-4-carboxylic acid amide;

1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-ethylaminoazetidine-3-carboxylic acid amide;

1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-isopropylaminoazetidine-3-carboxylic acid amide;

3-amino-1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-azetidine-3-carboxylic acid amide;

1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-methylaminoazetidine-3-carboxylic acid amide;

1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-dimethylaminoazetidine-3-carboxylic acid amide;

1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-isopropylaminoazetidine-3-carboxylic acid amide;

1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-4-ethylaminopiperidine-4-carboxylic acid amide;

1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-ethylaminoazetidine-3-carboxylic acid amide; and

1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-methylaminoazetidine-3-carboxylic acid amide;

a pharmaceutically acceptable salt thereof.

20(previously presented). The compound of Claim 19 selected from the group consisting of

1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-4-ethylaminopiperidine-4-carboxylic acid amide;

1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-ethylaminoazetidine-3-carboxylic acid amide;

1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-isopropylaminoazetidine-3-carboxylic acid amide;

3-amino-1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-azetidine-3-carboxylic acid amide;

1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-methylaminoazetidine-3-carboxylic acid amide;

1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-isopropylaminoazetidine-3-carboxylic acid amide;

1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-4-ethylaminopiperidine-4-carboxylic acid amide; and

1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-ethylaminoazetidine-3-carboxylic acid amide;

a pharmaceutically acceptable salt thereof.

21(previously presented). The compound of Claim 11 wherein

R^{4b}, $R^{4b'}$, R^{4f}, and $R^{4f'}$ are all hydrogen;

R^{4d} is hydrogen, hydroxy, amino, or a chemical moiety selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, acyloxy, acyl, $(C_1\text{-}C_3)$alkyl-O-C(O)-, $(C_1\text{-}C_6)$alkylamino-, and di$(C_1\text{-}C_4)$alkylamino-, where said moiety is optionally substituted with one or more substituents; and

$R^{4d'}$ is hydrogen, or a chemical moiety selected from the group consisting of $(C_1\text{-}C_6)$alkyl, aryl and heteroaryl, where said moiety is optionally substituted with one or more substituents;

a pharmaceutically acceptable salt thereof.

22(previously presented). The compound of Claim 21 wherein

X is a bond or -C(R^{4c})($R^{4c'}$)-, where R^{4c} and $R^{4c'}$ are each independently hydrogen or an optionally substituted $(C_1\text{-}C_6)$alkyl, or either R^{4c} or $R^{4c'}$ taken together with R^{4e} or $R^{4e'}$ forms a bond, a methylene bridge or an ethylene bridge; and

Z is a bond or -C(R^{4e})($R^{4e'}$)-, where R^{4e} and $R^{4e'}$ are each independently hydrogen or an optionally substituted $(C_1\text{-}C_6)$alkyl, or either R^{4e} or $R^{4e'}$ taken together with R^{4c} or $R^{4c'}$ forms a bond, a methylene bridge or an ethylene bridge;

a pharmaceutically acceptable salt thereof.

23(previously presented). The compound of Claim 22 wherein

R^{4c} and $R^{4c'}$ are each hydrogen or either R^{4c} or $R^{4c'}$ taken together with R^{4e} or $R^{4e'}$ forms a bond;

R^{4d} is hydrogen, hydroxy, amino, or a chemical moiety selected from the group consisting of $(C_1\text{-}C_6)$alkoxy, acyl, $(C_1\text{-}C_6)$alkylamino-, and di$(C_1\text{-}C_4)$alkylamino-;

$R^{4d'}$ is hydrogen, or a chemical moiety selected from the group consisting of $(C_1\text{-}C_6)$alkyl and aryl, where said moiety is optionally substituted with one or more substituents; and

R^{4e} and $R^{4e'}$ are hydrogen or either R^{4e} or $R^{4e'}$ taken together with R^{4c} or $R^{4c'}$ forms a bond;

a pharmaceutically acceptable salt thereof.

24(previously presented). The compound of Claim 21, 22, or 23 wherein R^1 and R^2 are each independently a phenyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$alkyl, halo-substituted $(C_1\text{-}C_4)$alkyl, and cyano;

a pharmaceutically acceptable salt thereof.

25(previously presented). The compound of Claim 24 wherein R^1 and R^2 are each independently a phenyl substituted with 1 to 2 substituents independently selected from the group consisting of chloro, fluoro, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$alkyl, fluoro-substituted $(C_1\text{-}C_4)$alkyl), and cyano;

a pharmaceutically acceptable salt thereof.

26(previously presented). The compound of Claim 25 wherein R^1 is 2-chlorophenyl, 2-fluorophenyl, 2,4-dichlorophenyl, 2-fluoro-4-chlorophenyl, 2-chloro-4-fluorophenyl, or 2,4-difluorophenyl; and R^2 is 4-chlorophenyl or 4-fluorophenyl;

a pharmaceutically acceptable salt thereof.

27(previously presented). The compound of Claim 26 selected from the group consisting of

1-{1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-4-phenylpiperidin-4-yl}-ethanone;

3-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-azabicyclo[3.1.0]hex-6-ylamine;

1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-4-(4-fluorophenyl)-piperidin-4-ol; and

4-benzyl-1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-piperidin-4-ol;

a pharmaceutically acceptable salt thereof.

28(previously presented). The compound of Claim 11 wherein

R^{4b}, $R^{4b'}$, R^{4f}, and $R^{4f'}$ are all hydrogen; and

R^{4d} and $R^{4d'}$ taken together form a 3-6 membered partially or fully saturated heterocyclic ring, a 5-6 membered lactone ring, or a 4-6 membered lactam ring, where said heterocyclic ring, said lactone ring and said lactam ring are optionally substituted with one or more substituents and said lactone ring or said lactam ring optionally contains an additional heteroatom selected from oxygen, nitrogen or sulfur;

a pharmaceutically acceptable salt thereof.

29(previously presented). The compound of Claim 28 wherein

X is a bond, $-CH_2CH_2-$ or $-C(R^{4c})(R^{4c'})-$, where R^{4c} and $R^{4c'}$ are each independently hydrogen or an optionally substituted (C_1-C_6)alkyl, or either R^{4c} or $R^{4c'}$ taken together with R^{4e} or $R^{4e'}$ forms a bond, a methylene bridge or an ethylene bridge; and

Z is a bond, $-CH_2CH_2-$ or $-C(R^{4e})(R^{4e'})-$, where R^{4e} and $R^{4e'}$ are each independently hydrogen or an optionally substituted (C_1-C_6)alkyl, or either R^{4e} or $R^{4e'}$ taken together with R^{4c} or $R^{4c'}$ forms a bond, a methylene bridge or an ethylene bridge;

a pharmaceutically acceptable salt thereof.

30(previously presented). The compound of Claim 28 wherein R^{4d} and $R^{4d'}$ taken together form a 5-6 membered lactam ring, where said lactam ring is optionally substituted with one or more substituents and optionally contains an additional heteroatom selected from nitrogen or oxygen;

a pharmaceutically acceptable salt thereof.

31(previously presented). The compound of Claim 30 wherein

X is a bond or $-C(R^{4c})(R^{4c'})-$, where R^{4c} and $R^{4c'}$ are each hydrogen; and

Z is a bond or $-C(R^{4e})(R^{4e'})-$, where R^{4e} and $R^{4e'}$ are each hydrogen;

a pharmaceutically acceptable salt thereof.

32(previously presented). The compound of Claim 28, 29, 30 or 31 wherein R^1 and R^2 are each independently a phenyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$alkyl, halo-substituted $(C_1$-$C_4)$alkyl, and cyano;

a pharmaceutically acceptable salt thereof.

33(previously presented). The compound of Claim 32 wherein R^1 and R^2 are each independently a phenyl substituted with 1 to 2 substituents independently selected from the group consisting of chloro, fluoro, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$alkyl, fluoro-substituted $(C_1$-$C_4)$alkyl), and cyano;

a pharmaceutically acceptable salt thereof.

34(previously presented). The compound of Claim 33 wherein R^1 is 2-chlorophenyl, 2-fluorophenyl, 2,4-dichlorophenyl, 2-fluoro-4-chlorophenyl, 2-chloro-4-fluorophenyl, or 2,4-difluorophenyl; and R^2 is 4-chlorophenyl or 4-fluorophenyl;

a pharmaceutically acceptable salt thereof.

35(previously presented). The compound of Claim 34 selected from the group consisting of

2-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-5-methyl-2,5,7-triazaspiro[3.4]octan-8-one;

2-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-2,5,7-triazaspiro[3.4]octan-8-one;

8-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-1-isopropyl-1,3,8-triazaspiro[4.5]decan-4-one; and

2-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-6,6-dimethyl-2,5,7-triazaspiro[3.4]octan-8-one;

a pharmaceutically acceptable salt thereof.

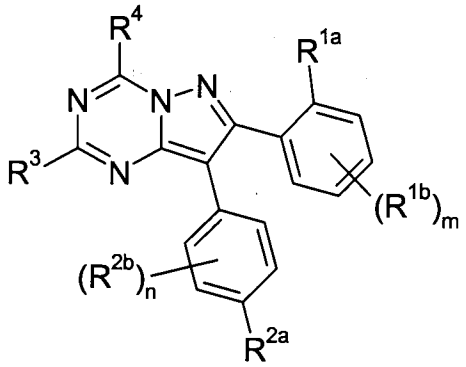
36(previously presented). The compound of Claim 35 which is

8-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-1-isopropyl-1,3,8-triazaspiro[4.5]decan-4-one;

a pharmaceutically acceptable salt thereof.

37-55 (cancelled).

56(previously presented). A compound of Formula (II)



(II)

wherein

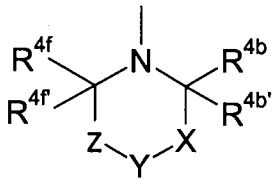
R^{1a}, R^{1b}, R^{2a}, and R^{2b} are each independently halo, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$alkyl, halo-substituted $(C_1\text{-}C_4)$alkyl, or cyano;

n and m are each independently 0, 1 or 2;

R^3 is hydrogen, $(C_1\text{-}C_4)$alkyl, halo-substituted $(C_1\text{-}C_4)$alkyl, or $(C_1\text{-}C_4)$alkoxy; and

R^4 is

(i) a group having Formula (IA)



IA

where R^{4a} is hydrogen or $(C_1\text{-}C_3)$alkyl;

R^{4b} and $R^{4b'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, (C_1-C_4)alkyl$)_2$N-C(O)-, (C_1-C_6)alkylamino-, $((C_1-C_4)$alkyl$)_2$amino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or either R^{4b} or $R^{4b'}$ taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge, or an ethylene bridge;

X is a bond, $-CH_2CH_2-$ or $-C(R^{4c})(R^{4c'})-$, where R^{4c} and $R^{4c'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, $((C_1-C_4)$alkyl$)_2$N-C(O)-, (C_1-C_6)alkylamino-, di(C_1-C_4)alkylamino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or either R^{4c} or $R^{4c'}$ taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge or an ethylene bridge;

Y is oxygen, sulfur, -C(O)-, or $-C(R^{4d})(R^{4d'})-$, where R^{4d} and $R^{4d'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, $((C_1-C_4)$alkyl$)_2$N-C(O)-, (C_1-C_6)alkylamino-, di(C_1-C_4)alkylamino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or R^{4d} and $R^{4d'}$ taken together form a 3-6 membered partially or fully saturated carbocyclic ring, a 3-6 membered partially or fully saturated heterocyclic ring, a 5-6 membered lactone ring, or a 4-6 membered lactam ring, where the carbocyclic ring, the

heterocyclic ring, the lactone ring and the lactam ring are optionally substituted with one or more substituents and the lactone ring and the lactam ring optionally contain an additional heteroatom selected from oxygen, nitrogen or sulfur, or

Y is $-NR^{4d''}-$, where $R^{4d''}$ is a hydrogen or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_3)alkylsulfonyl-, (C_1-C_3)alkylaminosulfonyl-, di(C_1-C_3)alkylaminosulfonyl-, acyl, (C_1-C_6)alkyl-O-C(O)-, aryl, and heteroaryl, where said moiety is optionally substituted with one or more substituents;

Z is a bond, $-CH_2CH_2-$, or $-C(R^{4e})(R^{4e'})-$, where R^{4e} and $R^{4e'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)-$, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, $((C_1-C_4)alkyl)_2N-C(O)-$, (C_1-C_6)alkylamino-, di(C_1-C_4)alkylamino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or either R^{4e} or $R^{4e'}$ taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge or an ethylene bridge; and

R^{4f} and $R^{4f'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)-$, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, $((C_1-C_4)alkyl)_2N-C(O)-$, (C_1-C_6)alkylamino-, di(C_1-C_4)alkylamino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a 3-6 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or either R^{4f} or $R^{4f'}$ taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge or an ethylene bridge;

a pharmaceutically acceptable salt thereof.

57(cancelled).

58(previously presented). The compound of Claim 56 wherein

R^{4b} is hydrogen, an optionally substituted $(C_1\text{-}C_3)$alkyl, or taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge, or an ethylene bridge;

$R^{4b'}$ is hydrogen, an optionally substituted $(C_1\text{-}C_3)$alkyl, or taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge, or an ethylene bridge;

R^{4f} is hydrogen, an optionally substituted $(C_1\text{-}C_3)$alkyl, or taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge, or an ethylene bridge; and

$R^{4f'}$ is hydrogen, an optionally substituted $(C_1\text{-}C_3)$alkyl, or taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge, or an ethylene bridge;

a pharmaceutically acceptable salt thereof.

59(previously presented). The compound of Claim 58 wherein

X is $-C(R^{4c})(R^{4c'})-$, where R^{4c} and $R^{4c'}$ are each independently hydrogen, $H_2NC(O)-$, or a chemical moiety selected from $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_4)$alkyl-NH-C(O)-, or $((C_1\text{-}C_4)\text{alkyl})_2N\text{-}C(O)-$, where said moiety is optionally substituted with one or more substituents,

or either R^{4c} or $R^{4c'}$ taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge or an ethylene bridge;

Y is $-NR^{4d''}-$, $R^{4d''}$ is a hydrogen or a chemical moiety selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_3)$alkylsulfonyl, $(C_1\text{-}C_3)$alkylaminosulfonyl, di$(C_1\text{-}C_3)$alkylaminosulfonyl, acyl, $(C_1\text{-}C_6)$alkyl-O-C(O)-, aryl, and heteroaryl, where said moiety is optionally substituted with one or more substituents;

Z is $-C(R^{4e})(R^{4e'})-$, where R^{4e} and $R^{4e'}$ are each independently hydrogen, $H_2NC(O)-$, or a chemical moiety selected from $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_4)$alkyl-NH-C(O)-, or $((C_1\text{-}C_4)\text{alkyl})_2N\text{-}C(O)-$, where said moiety is optionally substituted with one or more substituents,

or either R^{4e} or $R^{4e'}$ taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge or an ethylene bridge;

a pharmaceutically acceptable salt thereof.

60(previously presented). The compound of Claim 59 wherein $R^{4d''}$ is a hydrogen or a chemical moiety selected from the group consisting of $(C_1\text{-}C_3)$alkylsulfonyl, $(C_1\text{-}$

C_3)alkylaminosulfonyl, di(C_1-C_3)alkylaminosulfonyl, acyl, (C_1-C_6)alkyl-O-C(O)-, and heteroaryl, where said moiety is optionally substituted with one or more substituents;

a pharmaceutically acceptable salt thereof.

61(previously presented). The compound of Claim 60 wherein $R^{4d"}$ is a hydrogen or a chemical moiety selected from the group consisting of (C_1-C_3)alkylsulfonyl, (C_1-C_3)alkylaminosulfonyl, di(C_1-C_3)alkylaminosulfonyl, acyl, and (C_1-C_6)alkyl-O-C(O)-, where said moiety is optionally substituted with 1-3 fluorines,

or $R^{4d"}$ is a heteroaryl, where said heteroaryl is optionally substituted with 1 to 2 substituents independently selected from the group consisting of chloro, fluoro, (C_1-C_3)alkoxy, (C_1-C_3)alkyl, and fluoro-substituted (C_1-C_3)alkyl;

a pharmaceutically acceptable salt thereof.

62(previously presented). The compound of Claim 59, 60, or 61 wherein R^{1a}, R^{1b}, R^{2a} and R^{2b} are each independently selected from the group consisting of halo, (C_1-C_4)alkoxy, (C_1-C_4)alkyl, halo-substituted (C_1-C_4)alkyl, and cyano;

a pharmaceutically acceptable salt thereof.

63(previously presented). The compound of Claim 62 wherein R^{1a}, R^{1b}, R^{2a} and R^{2b} are each independently selected from the group consisting of chloro, fluoro, (C_1-C_4)alkoxy, (C_1-C_4)alkyl, fluoro-substituted (C_1-C_4)alkyl), and cyano; and

n and m are each independently 0 or 1;

a pharmaceutically acceptable salt thereof.

64(previously presented). The compound of Claim 58 wherein Y is -C(R^{4d})($R^{4d'}$)-, where R^{4d} is hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, (C_1-C_4)alkyl)$_2$N-C(O)-, (C_1-C_6)alkylamino-, ((C_1-C_4)alkyl)$_2$amino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a partially or fully

saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

$R^{4d'}$ is hydrogen, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, (C_1-C_4)alkyl$)_2$N-C(O)-, aryl, heteroaryl, a 3-6 membered partially or fully saturated heterocycle, and a partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents,

or R^{4d} and $R^{4d'}$ taken together form a 3-6 membered partially or fully saturated carbocyclic ring, a 3-6 membered partially or fully saturated heterocyclic ring, a 5-6 membered lactone ring, or a 4-6 membered lactam ring, where said carbocyclic ring, said heterocyclic ring, said lactone ring and said lactam ring are optionally substituted with one or more substituents and said lactone ring and said lactam ring optionally contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

a pharmaceutically acceptable salt thereof.

65(previously presented). The compound of Claim 64 wherein

R^{4b}, $R^{4b'}$, R^{4f}, and $R^{4f'}$ are all hydrogen;

R^{4d} is amino, (C_1-C_6)alkylamino, di(C_1-C_4)alkylamino, (C_3-C_6)cycloalkylamino, acylamino, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-; and

$R^{4d'}$ is (C_1-C_6)alkyl, $H_2NC(O)$-, (C_1-C_4)alkyl-NH-C(O)-, or $((C_1-C_4)$alkyl$)_2$N-C(O)-, or aryl;

a pharmaceutically acceptable salt thereof.

66(previously presented). The compound of Claim 65 wherein

X is a bond or $-C(R^{4c})(R^{4c'})$-, where R^{4c} and $R^{4c'}$ are each hydrogen; and

Z is a bond or $-C(R^{4e})(R^{4e'})$-, where R^{4e} and $R^{4e'}$ are each hydrogen;

a pharmaceutically acceptable salt thereof.

67(previously presented). The compound of Claim 66 wherein R^{4d} is amino, (C_1-C_6)alkylamino, di(C_1-C_4)alkylamino, (C_3-C_6)cycloalkylamino; and

$R^{4d'}$ is $H_2NC(O)$-, (C_1-C_4)alkyl-NH-C(O)-, or $((C_1-C_4)$alkyl$)_2$N-C(O)-;

a pharmaceutically acceptable salt thereof.

68(previously presented). The compound of Claim 64, 65, 66 or 67 wherein R^{1a}, R^{1b}, R^{2a}, and R^{2b} are each independently selected from the group consisting of halo, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$alkyl, halo-substituted $(C_1$-$C_4)$alkyl, and cyano;

a pharmaceutically acceptable salt thereof.

69(previously presented). The compound of Claim 68 wherein R^{1a}, R^{1b}, R^{2a}, and R^{2b} are each independently selected from the group consisting of chloro, fluoro, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$alkyl, fluoro-substituted $(C_1$-$C_4)$alkyl), and cyano; and

n and m are each independently selected from 0 or 1;

a pharmaceutically acceptable salt thereof.

70(previously presented). The compound of Claim 64 wherein

R^{4b}, $R^{4b'}$, R^{4f}, and $R^{4f'}$ are all hydrogen;

R^{4d} is hydrogen, hydroxy, amino, or a chemical moiety selected from the group consisting of $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, acyloxy, acyl, $(C_1$-$C_3)$alkyl-O-C(O)-, $(C_1$-$C_6)$alkylamino-, and di$(C_1$-$C_4)$alkylamino-, where said moiety is optionally substituted with one or more substituents; and

$R^{4d'}$ is hydrogen, or a chemical moiety selected from the group consisting of $(C_1$-$C_6)$alkyl, aryl and heteroaryl, where said moiety is optionally substituted with one or more substituents;

a pharmaceutically acceptable salt thereof.

71(previously presented). The compound of Claim 70 wherein

X is a bond or -C(R^{4c})($R^{4c'}$)-, where R^{4c} and $R^{4c'}$ are each independently hydrogen or an optionally substituted $(C_1$-$C_6)$alkyl, or either R^{4c} or $R^{4c'}$ taken together with R^{4e} or $R^{4e'}$ forms a bond, a methylene bridge or an ethylene bridge; and

Z is a bond or -C(R^{4e})($R^{4e'}$)-, where R^{4e} and $R^{4e'}$ are each independently hydrogen or an optionally substituted $(C_1$-$C_6)$alkyl, or either R^{4e} or $R^{4e'}$ taken together with R^{4c} or $R^{4c'}$ forms a bond, a methylene bridge or an ethylene bridge;

a pharmaceutically acceptable salt thereof.

72(previously presented). The compound of Claim 71 wherein

R^{4c} and $R^{4c'}$ are each hydrogen or either R^{4c} or $R^{4c'}$ taken together with R^{4e} or $R^{4e'}$ forms a bond;

R^{4d} is hydrogen, hydroxy, amino, or a chemical moiety selected from the group consisting of $(C_1$-$C_6)$alkoxy, acyl, $(C_1$-$C_6)$alkylamino-, and di$(C_1$-$C_4)$alkylamino-;

$R^{4d'}$ is hydrogen, or a chemical moiety selected from the group consisting of $(C_1$-$C_6)$alkyl and aryl, where said moiety is optionally substituted with one or more substituents; and

R^{4e} and $R^{4e'}$ are hydrogen or either R^{4e} or $R^{4e'}$ taken together with R^{4c} or $R^{4c'}$ forms a bond;

a pharmaceutically acceptable salt thereof.

73(previously presented). The compound of Claim 70, 71, or 72 wherein R^{1a}, R^{1b}, R^{2a}, and R^{2b} are each independently selected from the group consisting of halo, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$alkyl, halo-substituted $(C_1$-$C_4)$alkyl, and cyano;

a pharmaceutically acceptable salt thereof.

74(previously presented). The compound of Claim 73 wherein R^{1a}, R^{1b}, R^{2a}, and R^{2b} are each independently selected from the group consisting of chloro, fluoro, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$alkyl, fluoro-substituted $(C_1$-$C_4)$alkyl), and cyano; and

n and m are each independently 0 or 1;

a pharmaceutically acceptable salt thereof.

75(previously presented). The compound of Claim 64 wherein

R^{4b}, $R^{4b'}$, R^{4f}, and $R^{4f'}$ are all hydrogen; and

R^{4d} and $R^{4d'}$ taken together form a 3-6 membered partially or fully saturated carbocyclic ring, a 3-6 membered partially or fully saturated heterocyclic ring, a 5-6 membered lactone ring, or a 4-6 membered lactam ring, where said carbocyclic ring, said heterocyclic ring, said lactone ring and said lactam ring are optionally substituted with one or more substituents and said lactone ring or said lactam ring optionally contains an additional heteroatom selected from oxygen, nitrogen or sulfur;

a pharmaceutically acceptable salt thereof.

76(previously presented). The compound of Claim 75 wherein

X is a bond, $-CH_2CH_2-$ or $-C(R^{4c})(R^{4c'})-$, where R^{4c} and $R^{4c'}$ are each independently hydrogen or an optionally substituted (C_1-C_6)alkyl, or either R^{4c} or $R^{4c'}$ taken together with R^{4e} or $R^{4e'}$ forms a bond, a methylene bridge or an ethylene bridge; and

Z is a bond, $-CH_2CH_2-$ or $-C(R^{4e})(R^{4e'})-$, where R^{4e} and $R^{4e'}$ are each independently hydrogen or an optionally substituted (C_1-C_6)alkyl, or either R^{4e} or $R^{4e'}$ taken together with R^{4c} or $R^{4c'}$ forms a bond, a methylene bridge or an ethylene bridge;

a pharmaceutically acceptable salt thereof.

77(previously presented). The compound of Claim 76 wherein R^{4d} and $R^{4d'}$ taken together form a 5-6 membered lactam ring, where said lactam ring is optionally substituted with one or more substituents and optionally contains an additional heteroatom selected from nitrogen or oxygen;

a pharmaceutically acceptable salt thereof.

78(previously presented). The compound of Claim 77 wherein

X is a bond or $-C(R^{4c})(R^{4c'})-$, where R^{4c} and $R^{4c'}$ are each hydrogen; and

Z is a bond or $-C(R^{4e})(R^{4e'})-$, where R^{4e} and $R^{4e'}$ are each hydrogen;

a pharmaceutically acceptable salt thereof.

79(previously presented). The compound of Claim 75, 76, 77 or 78 wherein R^{1a}, R^{1b}, R^{2a}, and R^{2b} are each independently selected from the group consisting of halo, (C_1-C_4)alkoxy, (C_1-C_4)alkyl, halo-substituted (C_1-C_4)alkyl, and cyano;

a pharmaceutically acceptable salt thereof.

80(previously presented). The compound of Claim 79 wherein R^{1a}, R^{1b}, R^{2a}, and R^{2b} are each independently selected from the group consisting of chloro, fluoro, (C_1-C_4)alkoxy, (C_1-C_4)alkyl, fluoro-substituted (C_1-C_4)alkyl), and cyano;

n and m are each independently 0 or 1;

a pharmaceutically acceptable salt thereof.

81-96(cancelled).

97(previously presented). A pharmaceutical composition comprising (1) a compound of Claim 1, or a pharmaceutically acceptable salt thereof; and (2) a pharmaceutically acceptable excipient, diluent, or carrier.

98-100(cancelled).

101(previously presented). A method for treating obesity in animals comprising the step of administering to an animal in need of such treatment a therapeutically effective amount of a compound of Claim 1_

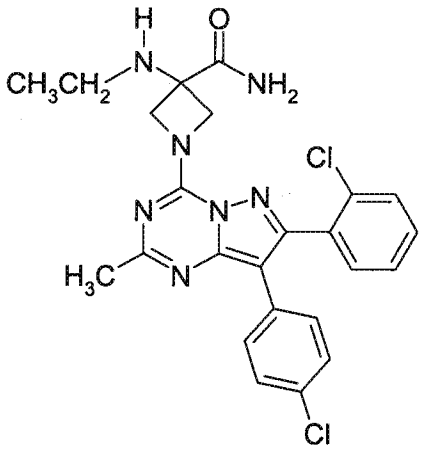
a pharmaceutically acceptable salt thereof.

102-107(cancelled).

108(previously presented). A method for treating obesity in an animal comprising the step of administering to an animal in need of such treatment a therapeutically effective amount of a pharmaceutical composition of Claim 97.

109-119(cancelled).

120(previously presented). A compound having the structure



121(previously presented). A compound which is 1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-ethylaminoazetidine-3-carboxylic acid amide;

or a pharmaceutically acceptable salt thereof.

EVIDENCE APPENDIX

No evidence was submitted during the prosecution of this application.

RELATED PROCEEDINGS APPENDIX

No related co-pending Interferences or Appeals in the U.S. Patent & Trademark Office.